Remarks and Arguments

Claims 1-12 were presented for examination. Claims 1 and 12 have been amended. Claims 13-17 were withdrawn from consideration.

Claim 8 was rejected under 35 U.S.C. §112, second paragraph, for lack of antecedent basis for the limitation "the mass spectrometric analysis" in line 3 because it was never established that the sample was subjected to mass spectrometric analysis. In response claim 1 has been amended, in lines 1-2, to recite "Method for the multidimensional separation of a biosubstance mixture prior to subjecting the mixture to a mass spectrometric analysis ..." thereby providing an antecedent basis for the recitation in claim 8.

Claim 12 was rejected under 35 U.S.C. §112, second paragraph, for lack of clarity concerning what method step the claim was trying to limit because, although the claim recites preparations for a mass spectrometric analysis, it does not recite a mass spectrometric analysis. In response, claim 12 has been amended to clarify it by indicating that it recites additional steps of transferring at least one of the separated fractions to a MALDI plate with a pipetting robot in order to perform the mass spectrometric analysis now recited in amended claim 1. It is believed that amended claim 12 is now clear and definite.

Claims 1-3, 7 and 8 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Publication No. US 2002/0139751 A1 (Zhang.) The examiner comments that the Zhang reference discloses all of the claimed limitations.

In the present invention, a complete sample mixture is contacted with a first solid surface and then the remaining mixtures of unbound biosubstances is sequentially contacted to further solid surfaces. Since the sample is not divided into sub-samples, rather the biosubstances stay in the remaining mixtures until they get bound to one of the solid surfaces.

The Zhang reference discloses a system in which capillary tubes containing affinity adsorbents are paired with cavities on a microchip that contain different affinity adsorbents (see, for example, Zhang Figures 5-8). Each one of the capillaries is paired with one cavity (Zhang Figure 9 and paragraph [0059]). The sample (biosubstance mixture) is divided into sub-samples and a single sub-sample is loaded onto one

capillary/cavity pair. The result of the arrangement is a multidimensional separation of the sample into multiple discrete fractions. The number of sub-samples (and capillary/cavity-pairs) is identical to the number of different discrete fractions. Therefore, in the Zhang reference all biosubstances, which are bound in one of the capillary/cavity-pairs, will be lost in all other pairs. Therefore, in the present invention, each fraction (and sub-fraction) contains more molecules of the respective biosubstance. The same applies to the fractionating dissolution.

Claim 1 has been amended to particularly point out this difference. Amended claim 1 now recites, in lines 3-6, for the fractionating binding "... separating the biosubstance mixture into multiple discrete fractions using a first fractionating binding by contacting the mixture to a first solid surface and sequentially contacting remaining mixtures of unbound biosubstances to further solid surfaces..." Amended claim 1 also recites, in lines 7-9, for the fractionating dissolution, "...separating the biosubstance mixture into multiple discrete fractions using ... a first fractionating dissolution by contacting the mixture to a surface and sequentially dissolving biosubstances through specially adjusted solvents ..." This wording is set forth in the present specification at paragraph [46] for the fractionating binding and at paragraph [29] for the fractionating dissolution. This processing of a mixture by sequential removal of fractions is not shown in Zhang. Therefore, claim 1 patentably distinguishes over the Zhang reference.

Claims 2-3, 7 and 8 are dependent on amended claim 1 and incorporate the limitations thereof. Therefore they also distinguish over the Zhang reference in the same manner as amended claim 1distinguishes over the Zhang reference.

Claims 1-3, 5, 6, 11 and 12 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Publication No. US 2002/0068366 A1 (LaDine.) The examiner comments that the LaDine references discloses all of the recited limitations.

The LaDine reference discloses another system for multidimensional separation of a sample into multiple discrete fractions using affinity binding to magnetic particles. Like the Zhang reference, in LaDine the sample is initially divided into sub-samples (see, for example, the step of protein separation in Figure 1, as described in paragraph [0028]). Each one of the sub-samples is brought into contact with magnetic particles derivatized with functional groups configured to bind biosubstances or a group of

biosubstances. The bound substances of each sub-sample are separated from the unbound substances and dissolved again to form separated samples that can be construed as fractions of the sample. Each of these separated samples is again divided and further fractionating is applied to the divided separated samples, for example using magnetic particles with different functional groups than in the first fractionating step (see LaDine paragraphs: [0029] and [0039]). However, the multidimensional fractionating of LaDine is in principle linked to the initial division of the sample into sub-samples. Thus, all biosubstances, which are initially placed in a particular sub-sample, will be lost in all other sub-samples. Therefore, in the present invention each fraction (and sub-fraction) contains more molecules of the respective biosubstance than the sub-samples of LaDine in the same manner as each fraction (and sub-fraction) contains more molecules of the respective biosubstance than the capillary/cavity pairs in Zhang. Consequently, amended claim 1 patentably distinguishes over the LaDine reference in the same manner as it distinguishes over the Zhang reference as discussed above.

Claims 2-3, 5, 6 11 and 12 are dependent on amended claim 1 and incorporate the limitations thereof. Therefore they also distinguish over the LaDine reference in the same manner as amended claim 1distinguishes over the LaDine reference.

Claim 4 has been rejected under 35 U.S.C. §103(a) as obvious over the LaDine reference in view of U.S. Patent No. 5,240,602 (Hammen.) The examiner comments that the LaDine reference discloses all of the recited limitation with the exception that it does not disclose coating the inner surface of microplate wells with substance binding layers. However, the examiner asserts that the Hammen reference discloses a method comprising the step of affixing affinity ligands to the wells of a microtiter plate, incubating the sample mixture with the ligands, and washing the ligands to remove the unbound species. The examiner concludes that it would have been obvious to combine the teachings of LaDine with those of Hammen in order to utilize immobilized ligands to bind the analyte of interest instead of using functionalized magnetic particles because immobilized ligands would be easier to process than particles that are suspended in the wells.

The Hammen references has been discussed in detail in a response filed on September 24, 2007. As noted there, only one separation is disclosed. Amended claim

1 clearly recites that at least two sequential separations are performed both with either affinity binding to a solid surface of solvent-based dissolution. These sequential separations are not disclosed in LaDine, as discussed above, or in Hammen. Thus, claim 1 patentably distinguishes over the combination of the LaDine and Hammen references. Claim 4 is dependent on claim 1 and incorporate the limitations thereof. Therefore, it distinguishes over the cited reference combination in the same manner as claim 1.

Claims 9 and 10 have been rejected under 35 U.S.C. §103(a) as obvious over the Zhang reference in view of U.S. Patent No. 5,240,604 (Cortes.) The examiner comments that the Zhang reference discloses all of the claimed limitations with the exception that it does not disclose the use of size exclusion chromatography. However, the examiner asserts that the Cortes reference discloses a chromatographic multidimensional separation system wherein the first separation dimension is achieved by size exclusion chromatography. The examiner concludes that it would have been obvious to combine the teachings of Zhang and Cortes in order to separate the proteins according to size.

The Cortes reference was also discussed in detail in the response filed on September 24th. The combination of Cortes with Zhang does not add to Zhang the sequential multi-dimensional fractionation by means of affinity binding to a solid surface or solvent-based dissolution that is discussed above with respect to Zhang and amended claim 1. Consequently, the combination of Zhang and Cortes does not teach or suggest the invention recited in claim 1. Since claims 9 and 10 are dependent on claim 1 and incorporate the limitations thereof, they distinguish over the cited reference in the same manner as claim 1.

In light of the forgoing amendments and remarks, this application is now believed in condition for allowance and a notice of allowance is earnestly solicited. If the examiner has any further questions regarding this amendment, he is invited to call

applicants' attorney at the number listed below. The examiner is hereby authorized to charge any fees or direct any payment under 37 C.F.R. §§1.17, 1.16 to Deposit Account number 50-3969.

Respectfully submitted

/paul e. kudirka/ Date: 2008-02-26

Paul E. Kudirka, Esq. Reg. No. 26,931
LAW OFFICES OF PAUL E. KUDIRKA
Customer Number 64967
Tel: (617) 357-0010 Fax: (617) 357-0035